MEMORANDUM

Date: 09/JUL/2008

SUBJECT: **Ingredient: Cymoxanil**
Title: Cymoxanil; Human Health Risk Assessment for Proposed Uses on Bulb Vegetables (Crop Group 3-07), Leafy Greens (Subgroup 4A), and Leaf Petioles (Subgroup 4B).

PC Code: 129106
Decision No.: 386112
Petition No.: 7E7282, 7E7283
Risk Assessment Type: Single Chemical, Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: 347653
Registration No.: 352-604
Regulatory Action: Section 3
Case No.: NA

CAS No.: 57966-95-7
40 CFR: 180.503

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1.0 Executive Summary

Cymoxanil is one of the technical active ingredients included in Tanos® Fungicide, a wettable granule formulation containing 25% ai cymoxanil + 25% ai famoxadone. Cymoxanil provides control of pathogen species of the order Peronosporales (e.g. Phytophthora, Plasmopara and Peronospora) in grapes, potatoes, tomatoes, hops, tobacco and cucurbits. Possible mode of action includes the inhibition of nucleic acid synthesis, mycelial respiration, membrane permeability and reduction of sporulation.

Use Profile: Cymoxanil is registered (Tanos® Fungicide; EPA Reg. No. 352-604) for use on caneberries, cucurbits, grapes, peppers, tomatoes, potatoes at 1.1 lb ai/A/year; and on hops at 0.75 lb ai/A/year. Registration is pending for use on leaf petioles at 0.75 lb ai/A/year; on bulb vegetables at 1.3 lb ai/A/year; on leafy vegetables (except spinach) at 1.5 lb ai/A/year and on spinach at 2.6 lb ai/A/year (DP Num: 349395, D. Rate, 26/JUN/2008).

Tolerances are established (40 CFR §180.503) for the fungicide cymoxanil (2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide) as follows. Tolerances for leaf vegetables, leafy petioles, bulb vegetables, and cilantro leaves are pending.

Tolerances <u>established</u> (40 CFR §180.503[a]) for the residues of the fungicide cymoxanil (2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide):

Caneberry	4.0 ppm
Hop, dried cones	7.0 ppm
Lettuce, head	4.0 ppm
Lychee	1.0 ppm
Potato	0.05 ppm
Vegetable, cucurbit, group 9	0.05 ppm
Vegetable, fruiting, group 8	0.2 ppm

Tolerances <u>established</u> (40 CFR §180.503[c]) for the residues of the fungicide cymoxanil (2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide):

Grape	0.10 ppm

Tolerances <u>pending</u> for the residues of the fungicide cymoxanil (2-cyano-*N*-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide)

Bulb vegetables, Subgroup 3-07A	1.1 ppm
Bulb vegetables, Subgroup 3-07B	0.05 ppm
Leaf vegetables, Subgroup 4A	19 ppm
Leafy Petioles, Subgroup 4B	6.0 ppm
Cilantro Leaves	19 ppm

Human Health Risk Assessment for Cymoxanil:

Toxicity/Hazard: Appropriate endpoints were identified for acute dietary, chronic dietary, incidental oral, dermal, and inhalation exposures for cymoxanil. The identified points of departure for cymoxanil are as follows:

An endpoint of concern (effect) attributable to a single dose was not identified in the database for acute risk to the general population, including infants and children. Therefore, quantification of acute risk to these populations is not required.

The acute dietary no-observed adverse-effect level (NOAEL) is 4 mg/kg/day (females 13-49 years). The lowest-observed adverse-effect level (LOAEL) is 8 mg/kg/day based on a developmental toxicity (rabbit) study.

The chronic dietary NOAEL is <0.8 mg/kg/day. The LOAEL is 1.3/0.8 mg/kg/day based on a chronic toxicity (dog) study.

The short-term oral NOAEL is 10.5 mg/kg/day. The LOAEL is 31.6/42.8 mg/kg/day (M/F) based on a 2-generation reproduction study in rat.

The intermediate-term oral NOAEL is 6.5 mg/kg/day. The LOAEL is 32.1 mg/kg/day (M/F) based on a 2-generation reproduction study in rat.

The short-and intermediate-term dermal NOAEL is 4 mg/kg/day. The LOAEL is 8 mg/kg/day (M/F) based on a developmental toxicity (rabbit) study.

The long-term dermal NOAEL is <0.8 mg/kg/day. The LOAEL is 1.3/0.8 mg/kg/day based on a chronic toxicity (dog) study.

The inhalation (short-, intermediate-term) NOAEL is 4 mg/kg/day. The LOAEL is 8 mg/kg/day based on a developmental toxicity (rabbit) study.

The long-term inhalation NOAEL is <0.8 mg/kg/day. The LOAEL is 1.3/0.8 mg/kg/day based on a chronic toxicity (dog) study.

Based on toxicological considerations by the Hazard Identification Assessment Review Committee (HIARC) (HED Doc. Date 02/JAN/2003) and updated toxicology review by RAB1 toxicologists (June 2008), recent studies, conservative residue assumptions used in the dietary risk assessment (currently no residential exposures), and the completeness of the residue chemistry and environmental fate databases (evaluated by the risk assessment team), the Food Quality Protection Act (FQPA) safety factor (SF) was reduced from 10X to 1X for acute exposure, incidental oral exposure (short- and intermediate-term), dermal exposure (short- and intermediate-term), and inhalation exposure (short- and intermediate-term). All other FQPA SFs remain at 10X.

Relating to the carcinogenic potential of cymoxanil, cymoxanil is classified as a "not likely" human carcinogen. The HIARC determined that cancer dietary risk concerns due to long-term

consumption of cymoxanil residues are adequately addressed by the chronic dietary exposure analysis using the reference dose; therefore, a separate cancer dietary exposure analysis was not performed.

Dietary Exposure (Food and Drinking Water): The dietary analyses were performed on cymoxanil to support new Section 3 registration requests for the proposed uses of cymoxanil on leafy petioles, leaf vegetables, bulb vegetables and cilantro leaves. The dietary exposure assessment was conducted for residues of cymoxanil in food and drinking water. The estimated drinking water concentrations (EDWCs) for cymoxanil residues used in the acute and the chronic dietary analyses were 9.3 ppm and 0.05 ppm, respectively. The EDWCs were estimated by using the screening model FIRST (FQPA Index Reservoir Screening Tool; v.1.1.0; dated 8/1/2001). These numbers were modeled from the use of cymoxanil on spinach.

An acute endpoint was selected for only one population subgroup, females 13-49 years. The acute dietary (food and drinking water) exposure to cymoxanil does not exceed the Agency's level of concern for the population subgroup, females 13-49 years. The acute dietary exposure estimate for this population subgroup at the 95th percentile of the exposure distribution is 89% of the acute Population-Adjusted Dose (aPAD).

The chronic dietary (food and drinking water) exposure to dichlobenil does not exceed the Agency's level of concern for the general U.S. population and all population subgroups. The chronic dietary exposure estimates are 48% chronic Population-Adjusted Dose (cPAD) for the general U.S. population and 74% of the cPAD for the highest exposed population subgroup (children 1-2 years).

With respect to *cancer risk*, HED classified cymoxanil as a "not likely" human carcinogen. The HIARC determined that cancer dietary risk concerns due to long-term consumption of cymoxanil residues are adequately addressed by the chronic dietary exposure analysis using the reference dose; therefore, a separate cancer dietary exposure analysis was not performed.

Residential Exposure:
Currently, there are no registered/proposed uses of cymoxanil that result in residential exposures.

Aggregate Risk:
The Agency conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Since there are no registered/proposed uses of cymoxanil that result in residential exposures, acute and chronic aggregate risk assessments were equal to the acute and chronic dietary estimates (food and water only).

Occupational Exposure/Risk:
Based on the proposed use patterns, cymoxanil may be applied aerially, by ground equipment and via sprinkler irrigation. ARIA believes the most highly exposed occupational pesticide handlers would be mixers/loaders using open-pour loading of a dry flowable formulation, applicators using open-cab airblast sprayers, applicators using open-cab ground-boom sprayers, and aerial applicators. Estimates of exposure are presented for each scenario. No cymoxanil

specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the Pesticide Handler Exposure Database (PHED) Version 1.1 (1998). For pesticide handlers, it is the Agency's standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as the "baseline" and the use of protective gloves or other personal protective equipment (PPE) as might be necessary. Margins of exposure (MOEs) are "combined" for dermal and inhalation exposures and risk since the toxicological endpoints are the same and were identified from the same study. MOEs of 100 are adequate to protect occupational pesticide handlers. In this case, all MOEs for pesticide handlers are >100 and, therefore, do not exceed the Agency's level of concern.

It is possible for agricultural workers to have post-application exposure to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-Entry Taskforce (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified Transfer Coefficients (TCs) (cm^2/hr) relative to the various activities which express the amount of foliar contact over time, during each of the activities identified. The highest (i.e., most conservative) TC for all of the proposed new uses is 2,500 cm^2/hr for hand harvesting or thinning of leafy green vegetables. As a "screening" level assessment, ARIA herein uses the TC of 2,500 cm^2/hr for hand harvesting or thinning. Lacking compound specific dislodgeable foliar residue (DFR) data, it is HED policy to assume 20% of the application rate is available as DFR on day zero after application. This is adapted from the OPP Science Policy Council for Exposure (ExpoSAC) standard operating procedure (SOP) No. 003 (07/MAY/1998 – Revised 07/AUG/2000). Estimated MOEs are >100; and, therefore, do not exceed the Agency's level of concern.

Environmental Justice Considerations:
Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://homer.ornl.gov/nuclearsafety/nsea/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy (as it relates to an imported crop), ARIA and HED estimate risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food consumption. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all proposed/registered food uses/tolerances of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure from traditional dietary patterns among specific subgroups.

Review of Human Research:
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies (listed in Appendix D) have been determined to require a review of their ethical conduct. They are also subject to review by the Human Studies Review Board. The listed studies have received the appropriate review.

Regulatory Recommendations and Data Deficiencies:

Pending submission of a revised Section F and product label (noted in Section 10.2), ARIA recommends for the tolerances listed in Appendix C.

Toxicology:
28-Day inhalation toxicity. Previously, this study was requested by the HIARC (2003) for further characterization of inhalation risk impacting occupational exposure. Due to the potential for inhalation exposure, there is a concern for toxicity by the inhalation route. However, this requirement will be waived for the purposes of this request, only, for the following reasons: 1) low acute inhalation toxicity (*i.e.* category IV); 2) the relatively low volatility of cymoxanil (1.5 x 10^{-4} Pa); 3) occupational exposure MOEs ≥770. Enough data is available to the Agency in the absence of this study to allow the Agency to move forward with a protective risk assessment. However, if the use pattern changes, this decision may be revisited.

Residue Chemistry:
The petitioner must submit a revised Section F to reflect the appropriate crop commodity definitions as listed in Appendix C and amend the label to prohibit the use of adjuvants.

Occupational/Residential:
None

2.0 Ingredient Profile

Cymoxanil is one of the technical active ingredients included in Tanos® Fungicide, a DF formulation containing 25% ai famoxadone + 25% ai cymoxanil. Cymoxanil provides control of pathogen species of the order Peronosporales (e.g., Phytophthora, Plasmopara and Peronospora) in grapes, potatoes, tomatoes, hops, tobacco, and cucurbits. Possible modes of action include the inhibition of nucleic acid synthesis, mycelial respiration, membrane permeability and reduction of sporulation.

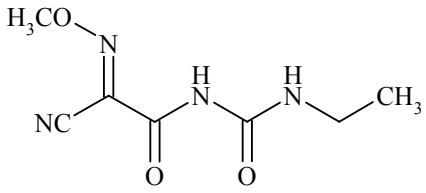
2.1 Summary of Proposed Uses

Table 2.1. Summary of Directions for Use of Cymoxanil.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Max. Single Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)
Bulb Vegetables, Group 3 (Including Chive, fresh leaves; Chive, Chinese, fresh leaves; Daylily, bulb; Elegans hosta; Fritillaria, bulb; Fritillaria, leaves; Garlic, bulb; Garlic, great-headed bulb; Garlic, serpent, bulb; Kurrat; Lady's leek; Leek, wild;					

Table 2.1. Summary of Directions for Use of Cymoxanil.					
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Max. Single Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)
Lily, bulb; Onion, Beltsville bunching; Onion, bulb; Onion, Chinese, bulb; Onion, fresh; Onion, green; Onion, macrostem; Onion, pearl; Onion, potato, bulb; Onion, tree, tops; Onion, Welsh; Shallot, bulb; and Shallot, fresh leaves)					
Foliar spray Ground (20 GPA), Aerial (min 5 GPA), or Chemigation	Tanos® [352-604]	0.16	Not specified	1.31	3
	Use Directions and Limitations: Begin applications prior to the onset of disease development. Make preventive applications on a 5- to 7-day schedule. Tanos® Fungicide must be tank-mixed with a contact fungicide which has a different mode of action (e.g., Manex copper, Kocide®, chlorothalonil, etc.) appropriate for the targeted disease. Do not alternate or tank mix with other Group 11 fungicides (all strobilurins or fenamidone) or with fungicides to which resistance has developed. In a cropping season, no more than 50% of the total applications should contain Tanos® Fungicide or other Group 11 fungicides.				
Leafy Greens, Subgroup 4A (Including: Amaranth (Chinese spinach); Arugula (roquette); Chervil; Chrysanthemum, edible-leaved; Chrysanthemum, garland; Cilantro, fresh leaves; Corn salad; Cress, garden; Cress, upland; Dandelion; Dock (sorrel); Endive (escarole); Lettuce, head; Lettuce, leaf; Orach; Parsley; Purslane, garden; Purslane, winter; Radicchio (red chicory); Spinach; Spinach, New Zealand; and Spinach, vine) **Leaf Petioles, Subgroup 4B** (Including Cardoon; celery; celery, Chinese; celtuce; fennel, Florence; rhubarb; Swiss chard)					
Foliar spray Ground (20 GPA), Aerial (5 GPA), or Chemigation	Tanos® [352-604]	0.16	Not specified	0.75 (for all crops except spinach) 1.31 (spinach)	1
	Use Directions and Limitations: Begin applications prior to the onset of disease development. Make preventive applications on a 5- to 7-day schedule. Tanos® Fungicide must be tank-mixed with a contact fungicide which has a different mode of action (e.g., copper, Kocide®, mancozeb, manzate®, chlorothalonil, etc.) appropriate for the targeted disease. In a cropping season, no more than 50% of the total applications should contain Tanos® Fungicide or other Group 11 fungicides. Do not make more than one application before alternating with a fungicide that has different mode of action.				
Caneberry Subgroup 13A (Includes Blackberries; Black and Red Raspberries; Loganberries; Wild Raspberries; and Cultivars/hybrids of These)					
Foliar spray Ground (20 GPA), Aerial (5 GPA), or Chemigation	Tanos® [352-604]	0.16	Not specified	1.125	0
	Use Directions and Limitations: Begin applications prior to the onset of disease development. Make preventive applications on a 5- to 7-day schedule. Tanos® Fungicide must be tank-mixed with a contact fungicide which has a different mode of action (e.g., Manex copper, Kocide®, chlorothalonil, etc.) appropriate for the targeted disease. Do not alternate or tank mix with other Group 11 fungicides (all strobilurins or fenamidone) or with fungicides to which resistance has developed. In a cropping season, no more than 50% of the total applications should contain Tanos® Fungicide or other Group 11 fungicides.				

2.2 Structure and Nomenclature

Table 2.1. Test Compound Nomenclature.	
Compound	
Common name	Cymoxanil
Company experimental name	DPX-T3217
IUPAC name	1-[(EZ)-2-cyano-2-methoxyiminoacetyl]-3-ethylurea
CAS name	2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide
CAS registry number	57966-95-7
End-use product (EP)	Tanos® Fungicide (EPA Reg. No. 352-604; a DF formulation containing 25% ai cymoxanil + 25% ai famoxadone); DPX-KP481

2.3 Physical and Chemical Properties

Table 2.3. Physiochemical Properties		
Parameter	Value	Reference
Molecular Weight	198.18	U.S. EPA Pesticide Fact Sheet (http://www.epa.gov/opprd001/factsheets/cymoxanil.pdf#search=%22cymoxanil%22)
Melting point/range	159-160°C	
pH	4.1	
Density	1.32 g/cm^3	
Water solubility (20°C)	0.9 g/Lin water, pH 5	
Solvent solubility (20°C to 25°C)	Acetone: 62.4 g/l Acetonitrile: 57.0 g/l Dichloromethane: 133 g/l Ethyl Acetate: 28.0 g/l Hexane: 0.037 g/l Methanol: 22.9 g/l Toluene: 5.29 g/l Octanol: 1.43 g/l	
Vapor pressure (25°C)	1.5 x 10^{-4} Pa at pH 5, 20°C	
Dissociation constant, pKa	9.7 ± 0.2	
Octanol/water partition coefficient, logP_{OW} (25°C)	3.9 at pH 5, 4.7 at pH 7	
UV/visible absorption spectrum	Not reported	

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

The following hazard profile was distilled from and updates the 4th Hazard Identification Assessment Review Committee (HIARC) report for cymoxanil (TXR# 0051440, 02/JAN/2003). Several studies have been added to the hazard database since that report and the last risk

assessment for cymoxanil (DP Num: 340367, D. Rate, *et.al.*, 17/MAY/2007. These studies are summarized in Tables A.1 and A.2 in Appendix A.

Cymoxanil has low acute toxicity (categories III and IV) via oral, dermal, inhalation, and ocular routes of exposure. It is a mild skin irritant and not a skin sensitizer. Systemic toxicity, as evidenced by decreased body weights, body weight gains, and food consumption, was observed in subchronic, chronic, developmental, reproductive and neurotoxicity studies across species. The dog appears to be the most sensitive species for cymoxanil-induced toxicity with the thymus gland identified as a target organ in this species during subchronic and chronic exposures. No evidence of immunotoxicity was observed following subchronic exposure of rats or mice up to 108/117 (M/F) or 218/552 (M/F) mg/kg/day, respectively. In a 21-day dermal toxicity study in rats, no systemic toxicity was observed up to the limit dose. In a subchronic neurotoxicity study in rats, systemic toxicity was observed at 102/137 mg/kg/day (M/F); however, no neurotoxicity and/or neuropathology were observed up to 224/333 mg/kg/day (M/F; highest dose tested). In addition, no evidence of neurotoxicity was observed in the developmental toxicity studies in rats or rabbits, the 2-generation reproduction study in rats, the subchronic or chronic dog studies, or the 18-month mouse carcinogenicity study. However, in the combined chronic toxicity/carcinogenicity study in rats, clinical signs of hyperactivity and aggressiveness in males (≥30.3 mg/kg/day), as well as retinal atrophy in both sexes (≥30.3 mg/kg/day) were observed.

Increased susceptibility of rats and rabbits was observed following *in utero* exposure to cymoxanil. In acceptable developmental toxicity studies in both of these species, developmental effects were seen at doses below those that caused maternal toxicity. In the rat developmental toxicity studies, skeletal anomalies, delays in skeletal ossification, and/or increases in overall malformations were observed at lower doses than those at which maternal toxicity was observed. In a rabbit developmental study, increased skeletal malformations were observed at 8 mg/kg/day (LOAEL), which was also below the maternal NOAEL of 32 mg/kg/day. Cleft palate was also observed in fetuses at 32 mg/kg/day. In the first 2-generation reproduction toxicity study (1993), decreased pup viability (PND 0-4) was observed at maternally toxic doses. In a second 2-generation reproduction toxicity study (2001), decreased body weight was observed during lactation in both F_1 and F_2 offspring at a dose that was lower than that at which parental toxicity was observed. The increased susceptibility of offspring observed in this study was concordant with the results obtained in the developmental toxicity studies. In a developmental neurotoxicity study, offspring toxicity – adverse effects included decreased pup survival, decreased pup weight and body weight gain during early lactation, increases in morphometric measurements (anterior/posterior cerebrum for males, cerebellar height for females) at PND 79-83, and decreased retention in the water maze task for adult females – was observed at the same dose as maternal toxicity (slight decreases in body weight, body weight gain during gestation, and food consumption). The LOAEL for both maternal animals and offspring was 100 mg/kg/day. No residual uncertainties exist in the database for pre-/post-natal toxicity, and the endpoints selected for risk assessment (section 3.5) are considered protective of effects observed in offspring in developmental and reproduction toxicity studies.

Cymoxanil was not carcinogenic in rats and mice and is classified as “not likely to be carcinogenic to humans”. The available studies indicate that cymoxanil is not mutagenic in bacteria or cultured mammalian cells. There is, however, evidence of clastogenic activity and

induction of unscheduled DNA synthesis *in vitro*. In contrast, cymoxanil was neither clastogenic nor aneugenic *in vivo* in mouse bone marrow cells and did not induce a genotoxic response in rat somatic or germinal cells. The negative results from the *in vivo* mouse bone marrow micronucleus assay support the lack of a carcinogenic effect in long-term rat and mouse feeding studies.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Cymoxanil was readily absorbed, and 86-94% of the administered dose was excreted in 96 hours. The majority of the administered dose was recovered in the urine (64-57%) and in the feces (16-24%). There were no sex-related differences in the absorption, distribution, and metabolism of cymoxanil. In urine about 37-55% of the dose was free and/or conjugated [^{14}C]glycine and 2 cyano-2-methoxyiminoacetic acid (IN-W3595; 7-33% of the dose). Parent was not isolated in urine. In feces intact [^{14}C]cymoxanil (< 1%) and IN W3595 were detected, but the majority of radioactivity was [^{14}C]glycine (9- 13%). Based on the data, the metabolic pathway involves hydrolysis of cymoxanil to IN- W3595, which is then degraded to glycine, which in turn is incorporated into natural constituents or further metabolized.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicology database for cymoxanil is adequate for assessing pre- and/or post-natal susceptibility. The following studies are available:

- Subchronic neurotoxicity study in rat (acceptable)
- Developmental toxicity studies in rat and rabbits (acceptable)
- 2-Generation reproduction toxicity study in rat (acceptable)
- Developmental neurotoxicity study in rat (acceptable)

3.3.2 Pre-and/or Postnatal Toxicity

As stated in section 3.1, there is an indication of increased susceptibility of rats and rabbits to *in utero* exposure to cymoxanil. In several developmental toxicity studies in the rat and rabbit, developmental toxicity was observed at doses that were lower than those that caused maternal toxicity. In the rat developmental toxicity studies, skeletal anomalies, delays in skeletal ossification, and/or increases in overall malformations were observed at lower doses than those at which maternal toxicity was observed. However, in the developmental neurotoxicity study in rat, offspring toxicity was observed at the same dose as maternal toxicity. In one rabbit developmental study, increased skeletal anomalies were observed at 8 mg/kg/day (LOAEL), which was below the maternal NOAEL of 32 mg/kg/day. In a second rabbit developmental toxicity study, an increased incidence of visceral and skeletal anomalies was observed at 25 mg/kg bw/day; a maternal LOAEL was not observed in this study. In the 2-generation reproduction toxicity study, decreased pup body weight was observed at a lower dose than that which caused toxicity in adults.

3.3.3 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

In the developmental and postnatal studies for which there is increased susceptibility, the effects are well characterized and conservative NOAELs were established for developmental and offspring effects. In addition, the doses selected for risk assessment are based on the lowest NOAELs from the developmental and reproductive toxicity studies, where appropriate, and are protective of any potential pre- and post-natal effects. Therefore, there are low levels of concern and no residual uncertainties for pre- and post-natal toxicity.

3.4 FQPA Safety Factor for Infants and Children

Based on toxicological considerations by the HIARC (HED Doc. Date 02/JAN/2003) and updated toxicology review by RAB1 toxicologists, recently reviewed studies, conservative residue assumptions used in the dietary risk assessment (currently no residential exposures), and the completeness of the residue chemistry and environmental fate databases (evaluated by the risk assessment team), the FQPA Safety Factor (SF) was reduced from 10X to 1X for acute exposure, incidental oral exposure (short- and intermediate-term), dermal exposure (short- and intermediate-term), and inhalation exposure (short- and intermediate-term) scenarios. The 10X FQPA SF is being retained, however, for chronic and long-term exposure scenarios (see section 3.5 below) in the form of a UF_L, due to the use of a LOAEL to extrapolate a NOAEL for the point of departure.

3.5 Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) - Females age 13-49

The acceptable developmental toxicity study in the rabbit was used to select the endpoint for establishing the acute RfD (aRfD) for females 13-49 years old. The aRfD is based on increased skeletal anomalies of the cervical and thoracic vertebrae and ribs observed in fetuses at the developmental LOAEL of 8 mg/kg/day. Because a clear NOAEL of 4 mg/kg/day was observed in the study and there are no residual uncertainties for pre-/post-natal toxicity, the FQPA safety factor (SF) is 1X.

3.5.2 Acute Reference Dose (aRfD) - General Population

An endpoint of concern (effect) attributable to a single dose was not identified in the database for acute risk to the general population, including infants and children. Therefore, quantification of acute risk to these populations is not required.

3.5.3 Chronic Reference Dose (cRfD)

The chronic toxicity study in the dog (2003) was used to select the endpoint for establishing the chronic RfD (cRfD). The cRfD is based on decreased absolute and relative thymus weights and histopathology of the thymus (thymic atrophy/involution) in males and decreased thymus weights in females seen at the LOAEL of 1.3/0.8 mg/kg/day (M/F). This LOAEL was the lowest

in the database. A NOAEL was not observed in this study; therefore, the FQPA SF (10X) was retained for the use of a LOAEL to extrapolate a NOAEL.

3.5.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Short-Term: A short-term incidental oral endpoint was selected from the second two-generation reproduction toxicity study in rats (2001). The endpoint was based on decreased body weight observed during lactation in both F_1 and F_2 offspring at the offspring LOAEL of 31.6/42.8 mg/kg/day (M/F). Because a clear offspring NOAEL of 10.5 mg/kg/day was observed in the study and there are no residual uncertainties for pre-/post-natal toxicity, the FQPA SF is 1X.

Intermediate-Term: An intermediate-term incidental oral endpoint was selected from the first two-generation reproductive toxicity study in rats (1993). The endpoint was based on reduced pre-mating body weight, body weight gain, and food consumption observed in P-generation males and decreased gestation and lactation body weight in F1 dams at the parental LOAEL of 32.1/40.6 mg/kg/day (M/F). Because a clear parental NOAEL of 6.5 mg/kg/day was observed in the study and there are no residual uncertainties for pre-/post-natal toxicity, the FQPA SF is 1X.

3.5.5 Dermal Absorption

An upper-bound estimate of dermal absorption was calculated by comparing the maternal LOAEL from the oral developmental toxicity study (rat) with the NOAEL from the dermal toxicity study (rat): [(75 mg/kg/day ÷ 1000 mg/kg/day) x 100%] = 7.5%. The HIARC report of Jan. 2, 2003 incorrectly calculated this to be 2.5%.

3.5.6 Dermal Exposure (Short-, Intermediate- and Long-Term)

Short-and intermediate-term dermal endpoints were selected from an acceptable developmental toxicity study in rabbits. Increased skeletal anomalies of the cervical and thoracic vertebrae and ribs were reported at the LOAEL of 8 mg/kg/day. The adverse effects observed in this study were considered appropriate for this exposure scenario, since they were not measured in the 21-day dermal study in rats. Because a clear developmental NOAEL of 4 mg/kg/day was observed in the study and there are no residual uncertainties for pre-/post-natal toxicity, the FQPA SF is 1X. Since endpoints from an oral study were selected for this exposure scenario, a 7.5% dermal absorption factor was used for route-to-route extrapolation.

The chronic toxicity study in the dog (2003) was used to select the endpoint for the long-term dermal exposure scenario. Decreased absolute and relative thymus weights and histopathology of the thymus (thymic atrophy/involution) in males and decreased thymus weights in females were observed at the LOAEL of 1.3/0.8 mg/kg/day (M/F). A NOAEL was not observed in this study; therefore, the FQPA SF (10X) was retained for the use of a LOAEL to extrapolate a NOAEL. Since an oral endpoint was selected for this exposure scenario, a 7.5% dermal absorption factor was used for route-to-route extrapolation.

3.5.7 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Short-and intermediate-term inhalation endpoints were selected from an acceptable developmental toxicity study in rabbits. Increased skeletal anomalies of the cervical and thoracic vertebrae and ribs were reported at the LOAEL of 8 mg/kg/day. Because a clear developmental NOAEL of 4 mg/kg/day was observed in the study and there are no residual uncertainties for pre-/post-natal toxicity in the database, the FQPA SF is 1X. The adverse effects observed in the oral developmental toxicity study in rabbits were considered appropriate for this exposure scenario in the absence of route-specific data. Accordingly, a 100% inhalation absorption factor was used for route-to-route extrapolation.

The chronic toxicity study in the dog (2003) was used to select the endpoint for the long-term inhalation exposure scenario. Decreased absolute and relative thymus weights and histopathology of the thymus (thymic atrophy/involution) in males and decreased thymus weights in females were observed at the LOAEL of 1.3/0.8 mg/kg/day (M/F). A NOAEL was not observed in this study; therefore, the FQPA SF (10X) was retained for the use of a LOAEL to extrapolate a NOAEL. Since an oral endpoint was selected in the absence of route-specific data, a 100% inhalation absorption factor was used for route-to-route extrapolation.

3.5.8 Level of Concern for Margin of Exposure

The target MOEs for occupational and non-dietary residential exposure risk assessments are as follows:

Table 3.5.8. Summary of Levels of Concern for Risk Assessment.

Route	Duration		
	Short-Term (1-30 days)	**Intermediate-Term (1-6 Months)**	**Long-Term (> 6 Months)**
Occupational (Worker) Exposure			
Dermal	100	100	1000
Inhalation	100	100	1000
Residential (Non-Dietary) Exposure			
Oral	100	100	N/A
Dermal	100	100	1000
Inhalation	100	100	1000

3.5.9 Recommendation for Aggregate Exposure Risk Assessments

An aggregated exposure risk assessment is not required since there are no residential uses for cymoxanil at this time.

3.5.10 Classification of Carcinogenic Potential

On December 2, 1997, the HIARC, in accordance with the Draft Proposed Guidelines for Carcinogen Risk Assessment (April 10, 1996) classified cymoxanil as "not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in mice and rats at doses that were judged to be adequate to assess the carcinogenic potential.

3.5.11 Summary of Toxicological Doses and Endpoints for Cymoxanil for Use in Human Risk Assessments

Table 3.5.11 Summary of Toxicological Doses and Endpoints for Cymoxanil for Use in Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population, including infants and children)	N/A	N/A	N/A	An endpoint of concern (effect) attributable to a single dose was not identified in the database. Quantification of acute risk to general population, including infants and children, is not required.
Acute Dietary (Females 13-49 years of age)	NOAEL = 4 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	aRfD = aPAD = 0.04 mg/kg/day	**Developmental toxicity (rabbit)** Offspring LOAEL = 8 mg/kg/day based on increased skeletal malformations of the cervical and thoracic vertebrae and ribs
Chronic Dietary (All populations)	NOAEL < 0.8 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF[1] = 10X (includes UF_L = 10X)	cRfD = cPAD = 0.0008 mg/kg/day	**Chronic toxicity (dog; 2003)** LOAEL = 1.3/0.8 mg/kg/day (M/F), based on decreased absolute and relative thymus weights and histopathology of the thymus (thymic atrophy/involution) in males and decreased thymus weights in females
Incidental Oral Short-Term (1-30 days)	NOAEL = 10.5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	**2-generation reproduction (rat; 2001)** Offspring LOAEL = 31.6/42.8 mg/kg/day (M/F) based on decreased body weight during lactation in both F_1 and F_2 generations
Incidental Oral Intermediate-Term (1-6 months)	NOAEL = 6.5 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	**2-generation reproduction (rat; 1993)** Parental LOAEL = 32.1 mg/kg/day (M/F) based on reduced premating body weight, body weight gain, and food consumption for P males; and decreased gestation and lactation body weights for F1 females
Dermal	NOAEL = 4	UF_A = 10X	Residential/	**Developmental toxicity**

Short-Term (1-30 days)	mg/kg/day (Dermal absorption = 7.5%)[2]	UF_H = 10X FQPA SF = 1X	Occupational LOC for MOE = 100	**(rabbit)** Offspring LOAEL = 8 mg/kg/day based on increased skeletal malformations of the cervical and thoracic vertebrae and ribs
Dermal Intermediate-Term (1-6 months)	NOAEL = 4 mg/kg/day (Dermal absorption = 7.5%)[2]	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential/ Occupational LOC for MOE = 100	**Developmental toxicity (rabbit)** Offspring LOAEL = 8 mg/kg/day based on increased skeletal malformations of the cervical and thoracic vertebrae and ribs
Dermal Long-Term (> 6 months)	NOAEL < 0.8 mg/kg/day (Dermal absorption = 7.5%)[2]	UF_A = 10X UF_H = 10X FQPA SF[1] = 10X (includes UF_L = 10X)	Residential/ Occupational LOC for MOE = 1000	**Chronic toxicity (dog; 2003)** LOAEL = 1.3/0.8 mg/kg/day (M/F), based on decreased absolute and relative thymus weights and histopathology of the thymus (thymic atrophy/involution) in males and decreased thymus weights in females
Inhalation Short-Term (1-30 days)	NOAEL = 4 mg/kg/day (100% inhalation absorption assumed)	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential/ Occupational LOC for MOE = 100	**Developmental toxicity (rabbit)** Offspring LOAEL = 8 mg/kg/day based on increased skeletal malformations of the cervical and thoracic vertebrae and ribs
Inhalation Intermediate-Term (1-6 months)	NOAEL = 4 mg/kg/day (100% inhalation absorption assumed)	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential/ Occupational LOC for MOE = 100	**Developmental toxicity (rabbit)** Offspring LOAEL = 8 mg/kg/day based on increased skeletal malformations of the cervical and thoracic vertebrae and ribs
Inhalation Long-Term (>6 months)	NOAEL < 0.8 mg/kg/day (100% inhalation absorption assumed)	UF_A = 10X UF_H = 10X FQPA SF[1] = 10X (includes UF_L = 10X)	Residential/ Occupational LOC for MOE = 1000	**Chronic toxicity (dog; 2003)** LOAEL = 1.3/0.8 mg/kg/day (M/F), based on decreased absolute and relative thymus weights and histopathology of the thymus (thymic atrophy/involution) in males and decreased thymus weights in females

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

[1]The 10X FQPA SF has been retained in the form of a UF_L to account for the use of a LOAEL to extrapolate a NOAEL

[2]An upper-bound estimate calculated as follows by comparing the maternal LOAEL from the oral developmental toxicity study (rat) with the NOAEL from the dermal toxicity study (rat): [(75 mg/kg/day ÷ 1000 mg/kg/day) x 100%] = 7.5%; the last HIARC report of Jan. 2, 2003 incorrectly calculated this to be 2.5%

3.6 Endocrine disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, cymoxanil may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

Based on the usage patterns and the lack of residential use sites, no incident reports are expected at this time.

5.0 Dietary Exposure/Risk Characterization

5.1 Pesticide Metabolism and Environmental Degradation

5.1.1 Metabolism in Primary Crops

The nature of the residue in grape, lettuce, potato, and tomato is adequately understood. In grapes, potatoes, and tomatoes, cymoxanil was metabolized primarily into [^{14}C]glycine, and further incorporated into the sugars fructose and glucose (DP Num: 241752, 246386, 247216, 247217, and 247210, G. Kramer/J. Rowell, 19/AUG/1998 and DP Num: 233933, G. Kramer, 19/NOV/1997). An *ad hoc* HED Metabolism Assessment Review Committee (MARC) met on 1/21/98 to discuss the toxicological significance of potential metabolites. It was decided that only the parent residue is of regulatory concern (DP Num: 242321, G. Kramer/S. Chun, 26/JAN/1998). HED, thus, concluded that cymoxanil *per se* is the only residue of concern for

tomatoes, potatoes, grapes, livestock, rotational crops, and drinking water.

Subsequent to the 1998 MARC meeting, the petitioner submitted a lettuce metabolism study. Metabolites IN-KQ960 and IN-KP533 were identified in the lettuce metabolism study but these metabolites were not detected in the tomato, grape, or potato metabolism studies. These results were presented to the HED MARC on 07/AUG/2001 to assess the toxicological significance of these metabolites and to determine which additional residues, if any, to regulate (DP Num: 276543, S. Levy/G. Kramer, 01/AUG/2001). The MARC determined that the nature of the residue is understood in leafy vegetables (DP Num: 276796, S. Levy, *et al.*, 30/AUG/2001). For the plant metabolism studies conducted to this point, the detection of metabolites IN-KQ960 and IN-KP533 is unique in lettuce. The MARC concluded that for the tolerance expression, the residue of concern in/on hops and leafy vegetables is cymoxanil *per se*. For risk assessment purposes, the metabolite IN-KQ960 must be included, along with the parent. When data on the metabolite is absent, the residue level of the metabolite will be based on the ratio (3.5:1) of IN-KQ960 to the parent in the lettuce ^{14}C metabolism study.

5.1.2 Metabolism in Rotational Crops

Following treatment of sandy loam soil with [^{14}C]cymoxanii at 1.08 lb ai/A (1.3x the maximum proposed seasonal rate), total radioactive residues, expressed as [^{14}C]cymoxanil equivalents, accumulated at levels >0.01 ppm in the raw agricultural commodities (RACs) of sugar beets planted 30 days after treatment (DAT) and the RACS of wheatplanted 30 and 120 DAT. Residues were <0.01 ppm in lettuce planted 30 and 120 DAT and in sugar beet RACs planted 120 DAT.

No cymoxanil or any previously identified metabolite was detected in any rotational crop commodity. No individual peak accounted for >0.02 ppm [^{14}C]cymoxanil equivalents.

5.1.3 Metabolism in Livestock

It was concluded at the pre-MARC meeting held on 21-JAN-1998 that only the parent (cymoxanil) was of regulatory and toxicological concern in livestock commodities (DP Num: 242321, G. Kramer, *et al*., 26/JAN/l998). No cymoxanil or related metabolites were detected in any goat matrices.

The following is shown for informational purposes of this meeting (DP Num: 242321, G. Kramer, *et al*., 26/JAN/l998). Following oral administration of [^{14}C]cymoxanil to a lactating goat at 10 ppm (~33x the maximum theoretical dietary burden) in the diet for 3 days, the total radioactive residues were 0.149-0.327 ppm in milk, 2.13 ppm in liver, 0.46 ppm in kidney, 0.08 ppm in muscle, and 0.07 ppm in fat. No cymoxanil or related metabolites were detected in any goat matrices. The majority of the radioactivity in liver (68.6% TRR, 1.46 ppm) and kidney (75.1% TRR, 0.34 ppm) was identified as [^{14}C]formic acid following hydrolysis, and the majority of the radioactivity in milk (45.5% TR.R, 0.13 ppm) was identified as [^{14}C]lactose. [^{14}C]Acetic acid was identified in liver (14.0% TRR, 0.30 ppm) and kidney (10.3% TRR, 0.05 ppm), and [^{14}C]glycerol was identified in liver (1.6% TRR, 0.04 ppm), kidney (8.8% TRR, 0.04 ppm), and milk (1.1% TRR, <0.01 ppm). In addition, the incorporation of radioactivity into

several fatty acids (such as capric, arachidonic, and laurie acid) was demonstrated in milk. Studies with rumen fluid indicated that metabolism of cymoxanil occurred via microorganisms in the rumen.

5.1.4 Analytical Methodology

An adequate high performance liquid chromatography (HPLC)/ultra violet (UV) method is available for the enforcement of proposed grape tolerance. Method AMR 3060-90 (MRIDs 43616541 and 43640504, DP Num: 218035 and 219844, G. Kramer, 25/APR/1996) was submitted in support of the previous tolerance petition (PP#5E04504) for imported grapes and tomatoes. Using this method, residues in/on crop samples are extracted by homogenization in ethyl acetate. Solids are removed by centrifugation, and the extract is concentrated and exchanged into acetone. After clean-up by SAX and silica column chromatography, the hexane/ethyl acetate eluate is exchanged into methanol. Cymoxanil is then analyzed using HPLC on a CN column with UV detection (254 nm). Column switching with a C-18 column is used if additional clean-up is required. The limit of quantitation (LOQ) was reported to be 0.05 ppm. Method AMR 3060-90 was successfully validated by an independent laboratory and had been forwarded to the analytical chemistry laboratory (ACL) for a pesticide method validation (PMV) (DP Num: 224541, G. Kramer, 01/APR/1996). The PMV was successful; however, the analytical chemistry branch (ACB) recommended (DP Num: 228837, G. Kramer, 05/AUG/1996) two revisions to the method (removal of directions to subtract the response of control samples and modification of the HPLC column specifications to indicate that a 25-cm column should be used instead of a 15-cm column). In response, the petitioner submitted Method AMR 3060-90 Revision No. 2 (MRID 44579103), and Agency review (DP Num: 241752, G. Kramer, 19/AUG/1998) of the re-written method concluded that it is adequate for enforcement method.

Another analytical method (AMR 3705-95, Revision No. 2) was also developed for data collection and enforcement purposes that can selectively quantitate both active ingredients (famoxadone and cymoxanil) either alone or in combination, using a common extraction procedure. The principles of the method include homogenization/extraction of sample matrices with aqueous acetonitrile (ACN). Cleanup steps involve solvent partitioning into hexane followed by passage through Florisil column or various solid-phase extraction (SPE) cartridges. The extracts are separated and famoxadone is quantitated by gas chromatography (GC)/ nitrogen/phosphorus detector (NPD) and cymoxanil by HPLC/UV with column switching. Enforcement (residue monitoring) methods of analysis are available for the quantitation of cymoxanil and famoxadone in plant matrices with adequate validation (independent laboratory validation (ILV)). The enforcement methods consist of HPLC/UV (cymoxanil) methodology. The LOQ was reported to be 0.05 ppm. Confirmation was provided by HPLC/mass spectrometry (MS), GC/MS or GC/MS/MS for residues of cymoxanil. An external standard was used as marker for retention time, response and calibration. The control chromatograms generally had no peaks above the chromatographic background in the area of analytical interest. There appeared to be no carryover to the following chromatograms. The method/detector response was linear ($r > 0.999$) within the range of 0.01-3.0 µg/mL. Percent recoveries were within guideline levels of 70-120% with acceptable standard deviations (±20%).

Extraction efficiency of incorporated ^{14}C-labelled cymoxanil was evaluated in plant matrices. The extraction efficiency of the residue extraction method as compared to the metabolism extraction methodology was adequate for cymoxanil in all matrices evaluated.

5.1.5 Environmental Degradation

Cymoxanil hydrolyzes rapidly under both alkaline and neutral media (34 hours at pH 7, 31 minutes at pH 9) but hydrolyzes slowly under acidic conditions (148 days at pH 5). Cymoxanil photo-degrades quickly (1.8 days) in near-surface aqueous media, and dissipates readily in aerobic and anaerobic soils with half lives on the order of hours to days. Major degradates formed from these processes generally degraded quickly with half-lives on the order of days. Field dissipation studies of cymoxanil showed dissipation half lives of from 1 day (in Maryland) to 8.7 days (in California) and also showed no detections of cymoxanil greater than 15 cm below grade for the duration of the test. Cymoxanil is moderately mobile with a mean K_{oc} of about 120 ml/g_{oc}.

5.1.6 Comparative Metabolic Profile

Cymoxanil was readily absorbed, and 86-94% of the administered dose was excreted in 96 hours. The majority of the administered dose was recovered in the urine (64-57%) and in the feces (16-24%). There were no sex-related differences in the absorption, distribution, and metabolism of cymoxanil. In urine about 37-55% of the dose was free and/or conjugated [^{14}C]glycine and 2 cyano-2-methoxyiminoacetic acid (IN-W3595; 7-33% of the dose). Parent was not isolated in urine. In feces intact [^{14}C]cymoxanil (< 1%) and IN W3595 were detected, but the majority of radioactivity was [^{14}C]glycine (9- 13%). Based on the data, the metabolic pathway involves hydrolysis of cymoxanil to IN- W3595, which is then degraded to glycine, which in turn is incorporated into natural constituents or further metabolized.

Metabolism of cymoxanil in ruminants appears to be similar to its metabolism in rats. The metabolism seems to proceed by hydrolysis of cymoxanil to IN- W3595, which, as previously discussed, is then converted to glycine and then incorporated into natural constituents or metabolized further. No cymoxanil or related metabolites were detected in any goat matrices. The majority of the radioactivity in liver (68.6% TRR, 1.46 ppm) and kidney (75.1% TRR, 0.34 ppm) was identified as [14C]formic acid following hydrolysis, and the majority of the radioactivity in milk (45.5% TRR, 0.13 ppm) was identified as [14C]lactose. [14C]Acetic acid was identified in liver (14.0% TRR, 0.30 ppm) and kidney (10.3% TRR, 0.05 ppm), and [14C]glycerol was identified in liver (1.6% TRR, 0.04 ppm), kidney (8.8% TRR, 0.04 ppm), and milk (1.1% TRR, <0.01 ppm). In addition, the incorporation of radioactivity into several fatty acids (such as capric, arachidonic, and lauric acid) was demonstrated in milk. Studies with rumen fluid indicated that metabolism of cymoxanil occurred via microorganisms in the rumen.

No cymoxanil or structurally related metabolites were detected in plant matrices (except leafy vegetables). In potatoes, for example, the majority of radioactivity was found to be associated with [^{14}C]glycine (78.5% TRR, 0.54 ppm), which was released upon strong acid hydrolysis of the aqueous potato extract. The incorporation of radioactivity into starch (at ~8% TRR, 0.06 ppm) was demonstrated via the release of [^{14}C]glucose following acid hydrolysis of

nonextractable residues

5.1.7 Toxicity Profile of Major Metabolites and Degradates

Little information is available on the toxicity of the major cymoxanil metabolite, IN-KQ960. The IN-KQ960 metabolite formed is unique to leafy vegetables appears not to be formed in the rat, livestock, or other plant matrices, and is not, therefore, part of the total toxic exposure for livestock and plant commodities (except leafy vegetables and hops). Based on chemical structure and limited detection in most matrices, IN-KQ960 is not likely to be more toxic than the parent; however, it is included in the risk assessment of leafy vegetable commodities.

5.1.8 Pesticide Metabolites and Degradates of Concern

For cymoxanil, the residues which are regulated in plant commodities are cymoxanil, *per se* (40 CFR §180.503). For risk assessment purposes, the residues of concern are cymoxanil for all commodities except leaf vegetables and hops, where metabolite, IN-KQ960 is included. No livestock tolerances have been established. In drinking water, residues of concern are cymoxanil.

Table 5.1.8. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Cymoxanil, *per se*, except for hops and leafy commoditites where cymoxanil + IN-KQ960 residues are included.	Cymoxanil, *per se*
	Rotational Crop	Cymoxanil, *per se*	Cymoxanil, *per se*
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water			Not Applicable

5.1.9 Drinking Water Residue Profile

Revised Drinking Water Assessment for the Proposed New Use of cymoxanil (Tanos®) on leafy greens, bulb vegetables, caneberries, cilantro leaves, onions, spinach and leaf lettuce, DP Num: 347651, A. McKinnon, 13/MAY/2008.

The drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) in the following memorandum: "Revised Drinking Water Assessment for the Proposed New Use of cymoxanil (Tanos®) on leafy greens, bulb vegetables, caneberries, cilantro leaves, onions, spinach and leaf lettuce" (DP Num: 347651, A. McKinnon, 13/MAY/2008) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Cymoxanil hydrolyzes rapidly under both alkaline and neutral media (34 hours at pH 7, 31 minutes at pH 9) but hydrolyzes slowly under acidic conditions (148 days at pH 5). Cymoxanil photodegrades quickly (1.8 days) in near-surface aqueous media, and dissipates readily in aerobic and anaerobic soils with half lives on the order of hours to days. Major degradates formed from these processes generally degraded quickly with half-lives on the order of days. Since the proposed new application rate for spinach (2.6 lb ai/A/year) is now considered the highest maximum use rate, the EDWCs for spinach represent the maximum exposures. The EDWC for cymoxanil in surface water and groundwater were calculated using the screening model FIRST (FQPA Index Reservoir Screening Tool; v.1.1.0; dated 8/1/2001) and the regression model SCI-GROW (Screening Concentration in Ground Water, v.2.3; dated 7/29/2003), respectively. The calculated EDWCs summarized in Table 5.1.9, below, are considered conservative. The model and its description are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Table 5.1.9. Summary of Maximum Estimated Drinking Water Concentrations (EDWCs) in Surface Water and Ground Water From the Maximum Allowed Application Rate and New Proposed Use Pattern for Cymoxanil.

Use Pattern	Use/Rate Modeled (lb ai/A)	Surface Water Acute EDWC (ppb)	Surface Water Chronic EDWC (ppb)	Groundwater EDWC (ppb)
Spinach	Aerial spray/0.16 x 16 applications; annual total of 2.6	9.3	0.05	1.8×10^{-3}

5.1.10 Food Residue Profile

47280501CFTonion.der, D. Rate, 24/MAR/2008
47280503CFTlettuce.der, D. Rate, 25/MAR/2008
47280502CFTspinach.der, D. Rate, 24/MAR/2008
47280601CFTcelery.der, D. Rate, 19/MAR/2008
Cymoxanil; *Application for Section 3 Registration on Bulb Vegetables (Crop Group 3), Leafy Greens (Subgroup 4A), and Leaf Petitioles (Subgroup 4B). Summary of Analytical Chemistry and Residue Data*, DP Num: 349395, D. Rate, 26/JUN/2008.

Tolerances are currently established for residues of the fungicide cymoxanil in/on various plant commodities, at levels ranging from 0.05 to 4.0 ppm (as listed in 40CFR §180.503[a]). Residue data from field trials conducted to support the existing registrations show that, generally, residues of cymoxanil are relatively low. The data submitted to support the tolerances on leafy vegetable commodities show that cymoxanil residues tend to cling to the unwashed RAC and are greatly dissipated with washing. The submitted magnitude of the residue data for the RACs of bulb vegetables, leafy greens, leaf petioles and cilantro leaves are adequate. There are adequate storage stability data to validate the storage conditions and intervals of samples collected for the field trials.

The Agency's *Guidance for Setting Pesticide Tolerances Based on Field Trial Data* was utilized for determining appropriate tolerance levels listed in Appendix C.

5.1.11 International Residue Limits

There are no Codex maximum residue limits (MRLs) established for residues of cymoxanil in crop or livestock commodities. Canadian and Mexican MRLs are established for cymoxanil (expressed as cymoxanil *per se*) but no limits are listed for the crop commodities addressed herein. An International Residue Limit (IRL) form is attached in Appendix C.

5.2 Dietary Exposure and Risk

Cymoxanil *Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessment[s] for the Section (3) Registration Action*, DP Num: 349396, D. Rate, 26/JUN/2008.

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 which use food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were performed to support Section 3 requests for the proposed new uses/tolerances in/on bulb onions, green onions, leaf vegetables, leafy petioles, and cilantro leaves.

5.2.1 Acute Dietary Exposure/Risk

An unrefined, acute dietary exposure assessment was performed for females 13-49 years old (no endpoint was identified for the general U.S. population or any other population subgroup) using tolerance level residues, 100 percent crop treated (%CT), and DEEM 7.81 default processing factors were used for all commodities except grapes. Processing factors for grape juice (1.4x) and raisins (1x) were derived from grape processing data (DP Num: 218035 and 219844, G. Kramer, 25/APR/1996). Estimated drinking water concentrations (EDWCs) were incorporated directly into the dietary assessment using the acute concentration for surface water generated by modeling at 9.3 ppb. This assessment indicates that the acute dietary exposure estimate (95^{th} percentile) is below the Agency's level of concern [<100% acute Population Adjusted Dose (aPAD)] for females 13-49 years old, utilizing 89% of the aPAD.

5.2.2 Chronic Dietary Exposure/Risk

A refined, chronic dietary exposure assessment was performed for the general U.S. population and various population subgroups using tolerance level residues or anticipated residues (field trial residues) and %CT (potatoes, head lettuce, peppers, tomatoes, watermelon, cucumber, pumpkin, and summer and winter squash). DEEM 7.81 default processing factors were used for all commodities except grapes. Processing factors for grape juice (1.4x) and raisins (1x) were derived from grape processing data (DP Num: 218035 and 219844, G. Kramer, 25/APR/1996). EDWCs were incorporated directly into the dietary assessment using the chronic concentration for surface water generated by modeling at 0.05 ppb. This assessment indicates that the chronic dietrary exposure estimates is below the Agency's level of concern [<100% chronic Population Adjusted Dose (cPAD)] for the general U.S. population (48% of the cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old utilizing 74% of the cPAD.

5.2.3 Cancer Dietary Risk

HED has classified cymoxanil as a "not likely" human carcinogen; therefore, there is no cancer risk associated with the proposed uses. The HIARC determined that cancer dietary risk concerns due to long-term consumption of cymoxanil residues are adequately addressed by the chronic dietary exposure analysis using the reference dose; therefore, a separate cancer dietary exposure analysis was not performed.

Table 5.2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Cymoxanil.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	NA		0.000383	48	NA	
All Infants (< 1 year old)			0.000404	51		
Children 1-2 years old			**0.000588**	**74**		
Children 3-5 years old			0.000521	65		
Children 6-12 years old			0.000348	44		
Youth 13-19 years old			0.000267	33		
Adults 20-49 years old			0.000401	50		
Adults 50+ years old			0.000357	45		
Females 13-49 years old	**0.035388**	**89**	0.000333	42		

NA = Not Applicable

*The values for the highest exposed population for each type of risk assessment are **bolded**.

5.3 Anticipated Residue and Percent Crop Treated (%CT) Information

Usage Report Package in Support of Registration for the Fungicide Cymoxanil (129106), DP Num: 333442, J. Carter, 02/NOV/2006.

As discussed in Section 5.2.2, the chronic dietary analysis was refined through the use of both anticipated residues and %CT. The %CT was provided by the Biological and Economic Analysis Division (BEAD) through screening level estimates of agricultural uses (SLUA). The anticipated residues used in the chronic analysis were calculated as average field trial residues from data submitted to the Agency. The Table 5.3 summarizes the residue data used in the chronic dietary (food and drinking water) analysis.

Table 5.3. Summary of Residue Refinement for Chronic Dietary Assessment for Cymoxanil.

RAC	Food Form	Existing / Proposed Tolerance, ppm	Chronic Residue Level, ppm	Percent Crop Treated (%CT)	Comments
Grape	RAC	0.1	0.0285	100	Chronic: Grape AR
Potato	RAC	0.05	0.05	10	Tolerance

Table 5.3. Summary of Residue Refinement for Chronic Dietary Assessment for Cymoxanil.					
RAC	Food Form	Existing / Proposed Tolerance, ppm	Chronic Residue Level, ppm	Percent Crop Treated (%CT)	Comments
Vegetable, cucurbits, Group 9	RAC	0.05	0.05	Cucumbers 10 Squash 1 Pumpkin 1 Watermelon 1	Tolerance
Eggplant	RAC	0.2	0.2	100	Tolerance
Okra	RAC	0.2	0.2	100	Tolerance
Pepper	RAC (Bell and Nonbell)	0.2	0.2	10	Tolerance
Tomatillo	RAC	0.2	0.2	100	Tolerance
Tomato	RAC	0.2	0.2	10	Tolerance
Caneberries, subgroup 13-07A	RAC	4.0	4.0	100	Tolerance
Cilantro (coriander), leaves	RAC	19	1.6	100	Spinach, washed (Parent + metabolite), AR
Chive	RAC	1.1	0.2	100	Green Onion AR
Hops	RAC	31.5	9.4	100	Hop (Average Field Trial + metabolite)
Leafy Greens, subgroup 4A	Amaranth, leafy	19	1.6	100	Spinach, washed (Parent + metabolite), AR
	Arugula	19	1.6	100	Spinach, washed (Parent + metabolite), AR
	Chrysanthemum, garland	19	1.6	100	Spinach, washed (Parent + metabolite), AR
	Cress, garden	19	1.6	100	Spinach, washed (Parent + metabolite), AR
	Cress, upland	19	1.6	100	Spinach, washed (Parent + metabolite), AR
	Dandelion, leaves	19	1.6	100	Spinach, washed (Parent + metabolite), AR
	endive	19	1.6	100	Spinach, washed (Parent + metabolite), AR
	Lettuce, head	19	3.15	10	Lettuce, head washed with wrapper reduction (Parent + metabolite), AR
	Lettuce, leaf	19	0.75	100	Lettuce, leaf washed (Parent + metabolite), AR
	Parsley, leaves	19	1.6	100	Spinach, washed (Parent + metabolite), AR

Table 5.3. Summary of Residue Refinement for Chronic Dietary Assessment for Cymoxanil.					
RAC	Food Form	Existing / Proposed Tolerance, ppm	Chronic Residue Level, ppm	Percent Crop Treated (%CT)	Comments
	Radicchio	19	3.15	100	Lettuce, head washed with wrapper reduction (Parent + metabolite), AR
	Spinach	19	1.6	100	Spinach, washed (Parent + metabolite), AR
Leaf Petioles, subgroup 4B	RACs	6.0	0.3	100	Celery, Washed (Parent + metabolite), AR
Onion, dry bulb, Subgroup 3-07A	RACs	0.05	0.05	100	Recommended Tolerance
	Dried	0.05	0.05	100	Recommended Tolerance
Onion, green, Subgroup 3-07B	RACs	1.1	0.2	100	Green Onion AR
Water, direct, all sources	NA	NA	0.05	NA	EFED
Water, indirect, all sources	NA	NA	0.05	NA	EFED

RAC = raw agricultural commodity.
AR = anticipated residue. All anticipated residues were calculated from average field trial data at the appropriate PHI under the additional conditions noted.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Currently, there are no registered/proposed uses of cymoxanil that result in residential exposures.

6.1 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for [chemical]. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

The Agency conducts aggregate exposure assessments by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Since there are no registered/proposed uses of cymoxanil that result in residential exposures, acute and chronic aggregate risk assessments were equal to the acute and chronic dietary estimates (food and water only).

7.1 Acute Aggregate Risk

In the case of cymoxanil, the acute aggregate risk is composed of exposures to cymoxanil residues in food and drinking water and is equivalent to the acute dietary risk discussed in Section 5.2. As noted in that section, the acute risk estimates do not exceed the Agency's level of concern for the population subgroup, females 13-49 years.

7.2 Long-Term Aggregate Risk

In the case of cymoxanil, the chronic aggregate risk is composed of exposures to cymoxanil residues in food and drinking water and is equivalent to the chronic dietary risk discussed in Section 5.2. As shown in Table 5.2, the chronic risk estimates do not exceed the Agency's level of concern for the general U.S. population and all population subgroups.

As noted earlier, cymoxanil is classified as a "not likely" human carcinogen. The HIARC determined that cancer risk concerns are adequately addressed by chronic exposure analysis using the reference dose; therefore, a separate cancer analysis was not required.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for cymoxanil and any other substances, and cymoxanil does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has assumed that cymoxanil does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

CYMOXANIL*- Nondietary Human Exposure/Risk Assessment for the Use of Cymoxanil Leafy Greens Crop Subgroup 4A, Bulb Vegetables Crop Group 3, Cilantro Leaves, Caneberries (Crop Subgroup 13A), and Leaf Petiole Vegetables, Crop Subgroup 4B*, DP Num: 349397, M. Dow, 05/MAR/2008.

9.1 Handler Risk

Based upon the proposed use pattern, ARIA believes the most highly exposed occupational pesticide handlers will be 1) mixer/loaders using open-pour loading of a dry flowable formulation, 2) applicators using open-cab ground-boom sprayers, 3) applicators using open-cab airblast sprayers, and 4) aerial applicators.

Occupational pesticide handlers may also be exposed while preparing sprinkler irrigation systems for use as an application vehicle. ARIA believes such activities are similar to those of a mixer/loader supporting aerial applications (i.e., preparing batch solutions to, in this case, be metered into an irrigation system's stream). Therefore, a separate assessment for persons preparing solutions for use in an irrigation system is not presented.

ARIA also believes occupational handlers will be exposed to short-term duration exposures (1 - 30 days). Although multiple applications are likely, they are not expected to be consecutive applications and should be alternated with other fungicides with differing modes of action. The treatment interval is 5 - 7 days. It is unlikely that handlers would be exposed continuously for 30 or more days (i.e., intermediate-term exposure). Therefore, only short-term duration risks were assessed.

Private (i.e., grower) applicators may perform all functions, that is, mix, load and apply the material. The ExpoSAC SOP Number 12 (29 March 2000) directs that although the same individual may perform all those tasks, they shall be assessed separately. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual. The available PHED and other exposure data support this and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, ground-boom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED/ARIA determine the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" **and the use of protective gloves** or other PPE as might be necessary. The product label directs applicators and other handlers to wear long-sleeved shirt, long pants, shoes plus socks and chemical-resistant gloves in Category A (such as butyl rubber, natural rubber, neoprene rubber or nitrile rubber), all $\geq$ 14 mils.

See Table 9.1 for a summary of exposures and risks to occupational pesticide handlers.

Table 9.1. Summary of Exposure & Risk to Occupational Handlers From Cymoxanil				
Unit Exposure[1] mg ai/lb handled	**Applic. Rate[2] lb ai/unit**	**Units Treated[3]**	**Avg. Daily Exposure[4] mg ai/kg bw/day**	**MOE[5]**
Mixer/Loader - Dry Flowable - Open Pour				
Dermal: SLNoGlove 0.066 LC SLWithGlove 0.066 HC Inhal. 0.00077 HC	0.156 lb ai/A	350 A/day	Dermal: SLNoGlove 0.0045 SLWithGlove 0.0045 Inhal. 0.0007	No Glove 770 With Glove 770
Applicator - Ground-boom - Open-cab				
Dermal: SLNoGlove 0.014 HC SLWithGlove 0.014 MC Inhal. 0.00074 HC	0.156 lb ai/A	200 A/day	Dermal: SLNoGlove 0.00055 SLWithGlove 0.00055 Inhal. 0.00039	No Glove 4,300 With Glove 4,300
Applicator - Air-blast - Open Cab				
Dermal: SLNoGlove 0.36 HC SLWithGlove 0.24 MC Inhal. 0.0045 HC	0.156 lb ai/A	40 A/day	Dermal: SLNoGlove 0.0028 SLWithGlove 0.0019 Inhal. 0.00047	No Glove 1,200 With Glove 1,700
Aerial Applicator (Pilots not required to wear gloves)				
Dermal: SLNoGlove 0.0050 MC Inhal. 0.000068 MC	0.156 lb ai/A	350 A/day	Dermal: SLNoGlove 0.00034 Inhal. 0.000062	No Glove 10,000

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from IR-4 submission.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; ExpoSAC SOP No. 9.1. Revised 5 July 2000;
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated * 7.5 % dermal absorption ÷ 60 kg Body Weight
5. MOE = Margin of Exposure = NOAEL ÷ ADD. The NOAELs for short- and intermediate-term dermal and inhalation exposure durations are 4.0 mg a.i./kg bw/day. They are identified from the same developmental toxicity study in the rabbit and cite the same toxic effects. Therefore dermal and inhalation exposures are summed then divided into NOAEL to determine Margin of Exposure.

9.2 Postapplication Risk

It is possible for agricultural workers to have post-application exposure to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified transfer coefficients (TC) (cm^2/hr) relative to the various activities which express the amount of foliar contact over time, during each of the activities identified. The highest (i.e., most conservative) TC for all the proposed new uses is 2,500 cm^2/hr for hand harvesting or thinning of leafy green vegetables. As a "screening" level assessment, ARIA herein uses the TC of 2,500 cm^2/hr for hand harvesting or thinning.

The TCs used in this assessment are from an interim TC SOP developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of HED's

ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20 % of the application rate is available as dislodgeable foliar residue on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (7 May 1998 - Revised 7 August 2000).

The following convention may be used to estimate post-application exposure.

Average Daily Dose (ADD) (mg a.i./kg bw/day) = DFR $\mu g/cm^2$ * TC cm^2/hr * hr/day * 0.001 mg/µg * 1/60 kg bw

and where:

Surrogate Dislodgeable Foliar Residue (DFR) = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * 4.54 x 10^8 µg/lb * 2.47 x 10^{-8} A/cm^2 .

0.156 lb a.i./A * 0.20 * $(1\text{-}0)^0$ * 4.54 x 10^8 µg/lb * 2.47 x10^{-8} A/cm^2 = 0.349 $\mu g/cm^2$, therefore,

0.349 $\mu g/cm^2$ * 2,500 cm^2/hr * 8 hr/day * 0.001 mg/µg * 0.075 (7.5 % dermal absorption) ÷ 60 kg bw = 0.0087 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 4.0 mg/kg bw/day ÷ 0.0087 mg/kg bw/day = **460.**

A MOE of 100 is adequate to protect agricultural workers from post-application exposures. The most conservative estimate (i.e., highest exposure/risk) of post-application exposure results in MOEs > 100. Therefore, the proposed risk does not exceed the Agency's level of concern.

9.3 Restricted Entry Interval (REI)

Cymoxanil is classified in Acute Toxicity Category III for acute dermal toxicity. It is classified in Toxicity Category IV for acute inhalation toxicity, primary eye irritation and primary skin irritation. It is not a dermal sensitizer. Therefore the interim worker protection standard (WPS) REI of 12 hours is adequate to protect agricultural workers from postapplication exposures to cymoxanil.

10.0 Data Needs and Label Recommendations

10.1 Toxicology

28-Day inhalation toxicity. Previously requested by the HIARC (2003) for further characterization of inhalation risk impacting occupational exposure, this study will be waived for

the proposed use pattern addressed herein. This requirement will be waived for the following reasons: 1) low acute inhalation toxicity (*i.e.* category IV); 2) the relatively low volatility of cymoxanil (1.5×10^{-4} Pa); 3) occupational exposure MOEs ≥770. Enough data is available to the Agency in the absence of this study to allow the Agency to move forward with a protective risk assessment. However, if the use pattern changes, this decision may be revisited.

10.2 Residue Chemistry

The petitioner must submit a revised Section F to reflect the appropriate crop commodity definitions as listed in Appendix C and amend the label to prohibit the use of adjuvants.

10.3 Occupational and Residential Exposure

None

References:

DP Num: 228837, G. Kramer, 05/AUG/1996
DP Num: 241752, 246386, 247216, 247217, and 247210, G. Kramer/J. Rowell, 19/AUG/1998
DP Num: 233933, G. Kramer, 19/NOV/1997
DP Num: 242321, G. Kramer, *et. al*., 26/JAN/l998
DP Num: 218035 and 219844, G. Kramer, 25/APR/1996
DP Num: 224541, G. Kramer, 01/APR/1996
DP Num: 228837, G. Kramer, 05/AUG/1996
DP Num: 241752, G. Kramer, 19/AUG/1998
DP Num: 347651, A. McKinnon, 13/MAY/2008
47280501CFTonion.der, D. Rate, 24/MAR/2008
47280503CFTlettuce.der, D. Rate, 25/MAR/2008
47280502CFTspinach.der, D. Rate, 24/MAR/2008
47280601CFTcelery.der, D. Rate, 19/MAR/2008
DP Num: 349395, D. Rate, 26/JUN/2008
DP Num: 218035 and 219844, G. Kramer, 25/APR/1996
DP Num: 349396, D. Rate, 26/JUN/2008
DP Num: 333442, J. Carter, 02/NOV/2006
DP Num: 349397, M. Dow, 05/MAR/2008
HED DOC. NO. 012457, J. Rowland, 21/JAN/1998
HED DOC. NO. 013879, M. Copley, 06/DEC/1999
TXR NO. 0050957, G. Reddy, 23/JUL/2002
TXR NO. 0051440, G. Reddy, 02/JAN/2003
TXR. No. 0050020, G. Kramer, 26/JAN/1998
DP Num: 276796, S. Levy, 30/AUG/2001
DP Num: 242321, G. Kramer, 26/JAN/1998

Appendix A: Toxicity Profile Tables

Table A.1. Acute Toxicity of Cymoxanil Technical Grade Active Ingredient (TGAI).				
Guideline No.	**Study Type**	**MRID NO.**	**Results**	**Toxicity Category**
870.1100	Acute Oral	43616512	LD_{50} = 960 mg/kg	III
870.1200	Acute Dermal	43616513	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation	42706303	LC_{50} = >5.06 mg/L	IV
870.2400	Primary Eye Irritation	43616514	Non- irritant	IV
870.2500	Primary Skin Irritation	43616515	Mild or slight irritant	IV
870.2600	Dermal sensitization	43640501	Non sensitizer	N/A

Table A.2. Subchronic, Chronic, and Geno- Toxicity Profile for Cymoxanil.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/Doses**	**Results**
870.3100	90-Day oral Toxicity rodents (rat)	43616516 (1993) **Acceptable/Guideline** 0, 100, 750, 1500, or 3000 ppm, M: 0, 6.54, 47.6, 102, or 224 mg/kg/day F: 0, 8, 59.9, 137, or 333 mg/kg/day	**Systemic Toxicity NOAEL = 47.6 mg/kg/day in males and 59.9 mg/kg/day in females** **Systemic Toxicity LOAEL= 102 mg/kg/day in males and 137 mg/kg/day in females,** based on decreases in body weights, body weight gains and food efficiency in the females, and body weight decreases and testicular and epididymal changes in males.
870.3100	90-Day oral Toxicity rodents (rat)	46749803 (1999) **Acceptable/Non-guideline** 0, 500, 1000, or 2000 ppm, M: 0, 42.6, 85.1, or 173.9 mg/kg/day F: 0, 48.1, 97.8, or 186.7 mg/kg/day	NOAEL = 1000 ppm (85 mg/kg/day) in males and 2000 ppm (187 mg/kg/day) in females LOAEL= 2000 ppm (174 mg/kg/day) in males based on reduced body weight and body weight gain; and not observed in females
870.3100	90-Day oral Toxicity rodents (mouse)	43616517 (1992) **Acceptable/Guideline** 0, 50, 500, 1750, 3500, or 7000 ppm M: 0, 8.25, 82.4, 294, 566, or 1306 mg/kg/day F: 0, 11.3, 121, 433, 846, or 1130 mg/kg/day	**Systemic Toxicity NOAEL = 8.25 mg/kg/day in males and 121 mg/kg/day in females** **Systemic Toxicity LOAEL= 82.4 mg/kg/day in males and 433 mg/kg/day in females,** based on statistically significant dose-related decreased body weights in males and increased absolute liver weights in females.
870.3100	90-Day oral Toxicity rodents (mouse)	46749804 (1999) **Unacceptable/guideline** 0, 15, 450, or 1350 ppm, M: 0, 28.7, 84.4, or 256.6 mg/kg/day F: 0, 32.9, 97.3, or 302.5 mg/kg/day	NOAEL = 450 ppm (84.4/97.3 mg/kg/day) [M/F] LOAEL= 1350 ppm (256.6/302.5 mg/kg/day) [M/F] based on reduced body weight gain and food efficiency
870.3150	90-Day oral toxicity in non-rodents (dog).	46749805 (1999) **Acceptable/Guideline** 0, 200, 400, or 800 ppm (0/0, 4.9/5.2, 9.7/9.9, or 14.2/15.5 mg/kg/day [M/F])	NOAEL not established LOAEL= 200 ppm (4.9/5.2 mg/kg/day) [M/F], based on decreased thymus weight
870.3150	90-Day oral toxicity in non-rodents (dog).	43640502 (1992) **Acceptable/Guideline** 0, 100, 200 ppm (0, 3, 5 mg/kg/day) for 13 weeks, or 250 ppm (5 mg/kg/day) for 2 weeks followed by 500 ppm (11 mg/kg/day) for 11 weeks	**Systemic Toxicity NOAEL** not established **Systemic Toxicity LOAEL= 3 mg/kg/day**, based on decreased body weights (13%) and food consumption in females.
870.3200	21/28-Day dermal toxicity	44180705 (1996)	**Systemic and Dermal Toxicity NOAEL = 1000 mg/kg/day**

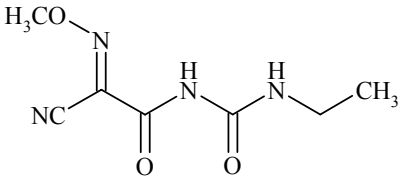
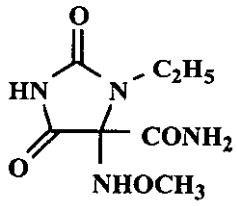
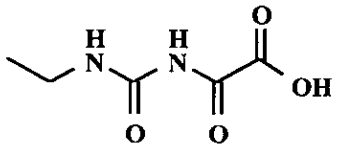
Table A.2. Subchronic, Chronic, and Geno- Toxicity Profile for Cymoxanil.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/Doses**	**Results**
	(rat)	**Acceptable/Guideline** 0, 50, 500 or 1000 mg/kg/day	**(HDT)** **Systemic and Dermal Toxicity LOAEL** was not established.
870.3700a	Prenatal developmental (rat)	43616524 (1993) **Acceptable/Guideline** 0, 10, 25, 75, or 150 mg/kg/day	**Maternal NOAEL = 25 mg/kg/day** **Maternal LOAEL= 75 mg/kg/day,** based upon reduced body weight, body weight change and food consumption **Developmental NOAEL = 10 mg/kg/day** **Developmental LOAEL = 25 mg/kg/day,** based upon significant increase in overall malformations, and generalized dose-related delay in skeletal ossification; at 75 and 150 mg/kg/day significant decrease in fetal body weights; at 150 mg/kg/day increased early resorptions resulting in reduced litter size.
870.3700a	Prenatal developmental (rat)	46749806 (1998) 0, 30, 60, or 120 mg/kg bw/day **Acceptable/Guideline**	Maternal NOAEL = 60 mg/kg/day Maternal LOAEL = 120 mg/kg/day based on reductions in body weight, body weight gain, and food intake. Developmental NOAEL not observed Developmental LOAEL = 30 mg/kg bw/day, based on increased incidences of skeletal anomalies (incomplete ossification of the supraoccipital and rudimentary rib #14).
870.3700b	Prenatal developmental (rabbit)	43640503 & 43616523 (1982) **Acceptable/Guideline** 0, 1, 4, 8, or 32 mg/kg/day	**Maternal NOAEL ≥32 mg/kg/day** **Maternal LOAEL** was not established **Developmental NOAEL = 4 mg/kg/day** **Developmental LOAEL = 8 mg/kg/day**, based upon an increase in skeletal anomalies of the cervical and thoracic vertebrae and ribs; at 32 mg/kg/day, cleft palate was also observed.
870.3700b	Prenatal developmental (rabbit)	43616522 (1981) **Unacceptable/Guideline,** however, in conjunction with MRIDs 43616521, 43616523 & 43640503 provides valuable information in selecting the maternal and developmental end-points. 0, 8, 16, or 32 mg/kg/day	**Maternal NOAEL = 16 mg/kg/day** **Maternal LOAEL = 32 mg/kg/day,** based upon increased incidence of clinical signs and body weight loss during first 4 days of treatment. **Developmental NOAEL**≤8 mg/kg/day (not established) **Developmental LOAEL = 8 mg/kg/day,** based upon an increase in skeletal anomalies of the cervical and thoracic vertebrae and ribs.
870.3700b	Prenatal developmental (rabbit)	43616521 (1980) **Unacceptable/Guideline,** however, in conjunction with MRIDs 43616522, 43616523 & 43640503 provides valuable information in selecting the maternal and developmental end-points. 0, 4, 8, or 16 mg/kg/day	**Maternal NOAEL = 16 mg/kg/day (HDT)** **Maternal LOAEL =** not determined. **Developmental NOAEL≥16 mg/kg/day (HDT))** **Developmental LOAEL =** not determined.
870.3700	Prenatal Developmental toxicity (rabbit; gavage)	46749807 (1999) **Acceptable/Non-guideline** 0, 5, 15, or 25 mg/kg bw/day	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL not observed Developmental NOAEL = 15 mg/kg/day Developmental LOAEL = 25 mg/kg bw/day, based on increased incidences of visceral [dilatation of the right and/or left ventricle(s) of the heart and unilateral or bilateral slight dilatation of the renal pelvis] and skeletal (accessory floating 13th rib) anomalies
870.3800	2-Generation Reproduction and Fertility Effects (rat)	43616520 (1993) **Acceptable/Guideline** 0, 100, 500, or 1500 ppm M: 0, 6.5, 32.1, or 97.9 mg/kg/day F: 0, 7.9, 40.6, or 130 mg/kg/day	**Systemic Toxicity NOAEL = 6.5 (M) and 7.9 (F) mg/kg/day** **Systemic Toxicity LOAEL = 32.1 (M) and 40.6 (F) mg/kg/day**, based on reduced pre-mating body weight, body weight gain, and food consumption for P males; and decreased gestation and lactation body weight for F1 females. **Reproductive Toxicity NOAEL = 97.9 mg/kg/day for**

Table A.2. Subchronic, Chronic, and Geno- Toxicity Profile for Cymoxanil.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/Doses**	**Results**
			males and 130 mg/kg/day for females. **Reproductive Toxicity LOAEL was not established.** **Offspring Toxicity NOAEL= 6.5 (M) and 7.9 (F) mg/kg/day** **Offspring Toxicity LOAEL= 32.1 (M) and 40.6 (F) mg/kg/day**, based upon decreased F1 pup viability on postnatal days 0-4 and on a significant reduction in F2b pup weight.
870.3800	2-Generation Reproduction and Fertility Effects (rat; dietary)	46749810 (2001) **Acceptable/Non-guideline** 0, 150, 450, or 1350 ppm [equal to 0/0, 10.5/14.9, 31.6/42.8, or 94/116.3 mg/kg bw/day (M/F)]	Parental NOAEL = 450 ppm (31.6/42.8 mg/kg/day) [M/F] Parental LOAEL = 1350 ppm (94/116.3 mg/kg/day [M/F] based on decreases in body weight, body weight gain, and food consumption in F0 and F1 generations. Reproductive NOAEL = 1350/450 ppm (94/42.8 mg/kg/day [M/F] Reproductive LOAEL = 116.3 (F) mg/kg/day based on decreased mean number of corpora lutea and mean number of implantations and increased post-implantation loss in F1 females (LOAEL not observed in males). Offspring NOAEL = 150 ppm (10.5/14.9 mg/kg/day) [M/F] Offspring LOAEL = 450 ppm (31.6/42.8 mg/kg/day [M/F] based on decreased body weight during lactation in both F1 and F2 generations.
870.4100	Chronic Toxicity (dog; dietary)	46749811 (2003) **Acceptable/Guideline** 0/0, 50/25, 100/50, or 200/100 ppm (equal to 0/0, 1.3/0.8, 2.8/1.4, or 5.6/2.9 mg/kg bw/day) (M/F)	NOAEL not observed. LOAEL = 50 ppm (1.3/0.8 mg/kg/day [M/F] based on decreased absolute and relative thymus weights and histopathology of the thymus (thymic atrophy/involution) (M) and decreased thymus weights (F)
870.4200	Carcinogenicity rodents (mouse)	43616519 (1994) **Acceptable/Guideline** 0, 30, 300, 1500, or 3000 ppm M: 0, 4.19, 42.0, 216, or 446 mg/kg/day F: 0, 5.83, 58.1, 298, or 582 mg/kg/day	**Systemic toxicity NOAEL = 4.19 mg/kg/day for males and 5.83 mg/kg/day for females** **Systemic toxicity LOAEL = 42 mg/kg/day for males and 58.1 mg/kg/day for females (HDT),** based upon increased frequency of sperm cyst/cystic dilation, tubular dilation and lymphoid aggregates in males and hyperplastic gastropathy in females. **No evidence of carcinogenicity.**
870.4200	Carcinogenicity (mouse; dietary)	46749808 (2002) 0, 60, 120, 600, or 1200 ppm [equivalent to 0/0, 9.5/9.5, 18.7/18.6, 91.4/92.4, or 178.3/179.8 mg/kg bw/day (M/F)] **Unacceptable/Guideline**	NOAEL = 1200 ppm (178.3/179.8) mg/kg/day (M/F) LOAEL not observed. The dose levels tested did not produce toxicity and the limit dose was not tested.
870.4300	Combined chronic toxicity/carcinogenicity rodents (rat)	43616525 (1994) **Acceptable/Guideline** 0, 50, 100, 700, or 2000 ppm M: 0, 1.98, 4.08, 30.3, or 90.1 mg/kg/day F: 0, 2.71, 5.36, 38.4, or 126 mg/kg/day	**Systemic toxicity NOAEL = 4.08 mg/kg/day for males and 5.36 mg/kg/day for females** **Systemic toxicity LOAEL = 30.3 mg/kg/day for males and 38.4 mg/kg/day for females,** based upon decreased body weight, body weight gain, and food efficiency, increased incidence of elongate spermatid degeneration and increased aggressiveness and/or hyperactivity in males and increased

Table A.2. Subchronic, Chronic, and Geno- Toxicity Profile for Cymoxanil.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/Doses**	**Results**
			incidence of non-neoplastic lesions of the lungs, liver, sciatic nerve and retinal atrophy in females. **No evidence of carcinogenicity.**
870.4300	Combined chronic toxicity/ carcinogenicity rodents (rat)	46749809 (2003) **Unacceptable/Guideline** 0, 100, 500, or 1200 ppm (0/0, 4.7/ 6.4, 23.5/31.6, 58.8/75.8mg/kg/day [M/F])	NOAEL = 100 ppm (4.7 mg/kg/day) for males and 500 ppm (31.6 mg/kg/day) for females LOAEL = 500 ppm (23.5 mg/kg/day) for males based on lymphoid hyperplasia of the rectum; and 1200 ppm (75.8 mg/kg/day) for females based upon suppurative bronchopneumonia. No evidence of carcinogenicity; insufficient dosing in females.
870.5100	Bacterial gene mutation assay	43616526 (1992) **Acceptable/Guideline** Salmonella typhimurium strains TA1535, TA97, TA98 and TA100 were exposed to Cymoxanil Technical (96.5-97.8%) at concentrations of 10-2500 µg/plate with or without S9 activation (both trials).	Cytotoxicity in all strains was seen at ≥750 µg/plate -S9 and ≥1000 µg/plate +S9. The positive controls induced the expected mutagenic responses in the appropriate tester strain. **There was, however, no evidence that the test material induced a mutagenic effect under any test condition.**
870.5300	*In vitro* mammalian cell gene mutation assay (CHO)	43616527 (1993) **Acceptable/Guideline** Chinese hamster ovary (CHO) cells were exposed to Cymoxanil Technical (96.5-97.8%) in dose ranges of 5-750 µg/mL -S9 (both trials) and S9-activated doses of 10-1500 µg/mL (Trials 1 and 2) or 250-1500 µg/mL (Trial 3).	Severe cytotoxicity was seen at 750 µg/mL -S9 and ≥1000 µg/mL +S9. The positive controls induced the expected mutagenic responses. **There was, however, no evidence that the test material was mutagenic at the HGPRT locus at any dose under any assay condition.**
870.5375	*In vitro* mammalian chromosomal aberration test	42706302 (1993) **Acceptable/Guideline** Human lymphocytes were exposed to Cymoxanil Technical (96.5-97.8%) in dose ranges of 100-1500 µg/mL ± S9 activation.	Significant and dose-related clastogenic effects were seen at 1250 and 1500 µg/mL -S9 activation and at 850, 1250 and 1500 µg/mL +S9 activation. **Cymoxanil is clastogenic both in the presence and absence of S9 activation.**
870.5395	Mammalian erythrocyte micronucleus test	43616528 (1993) **Acceptable/Guideline** Groups of six male and six female CR1:CD®-1(ICR)BR mice received single oral gavage administrations of 450 or 350 mg/kg Cymoxanil Technical (96.5-97.8%), respectively; lower doses (125 or 225 mg/kg) were administered to groups of five male and five female mice. High-dose group were sacrificed at 24, 48 and 72 hours post-administration; mice in the low- and mid-dose groups were sacrificed 24 hours post-dosing.	Death occurred in 6/18 high-dose (350 mg/kg) females. Other signs of compound toxicity noted in the high-dose males and females included abnormal gait, lethargy and tremors. Suggestive evidence of bone marrow cytotoxicity was seen in the high-dose females at the 48-hour cell harvest and in the high-dose males at the 24-hour harvest. The positive control induced the expected high yield of MPEs in males and females. **There was, however, no evidence that the test material induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.**
870.5550	Unscheduled DNA synthesis in mammalian cells in culture	42706301 (1993) **Acceptable/Guideline** Primary rat hepatocytes were exposed to Cymoxanil Technical (96.5-97.8%) at dose levels of 5 to 500 µg/mL	Cytotoxicity was observed at levels ≥500 µg/mL. **Cymoxanil tested positive over 5 to 500 µg/mL range.**
		43616529(1994)	

Table A.2. Subchronic, Chronic, and Geno- Toxicity Profile for Cymoxanil.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/Doses**	**Results**
870.5550	Unscheduled DNA synthesis in mammalian cells in culture	**Acceptable/Guideline** Groups of five male CR1:CD®BR rats were administered single oral gavage doses of 500 or 1000 mg/kg Cymoxanil Technical (96.5-97.8%) in 0.5% methyl cellulose. At 2 and 16 hours post-treatment hepatocytes and spermatocytes were scored for UDS.	Clinical signs of toxicity noted in both treatment groups included death (3 of 10 rats at 1000 mg/kg; 1 of 10 rats at 500 mg/kg), lethargy, prostrate posture, labored or rapid respiration, tremors, diarrhea and abnormal gait (both study groups). Cytotoxicity was not observed in either target tissue. Positive controls responded appropriately. **There was, however, no evidence that the test material induced a genotoxic response in either tissue at any dose or sacrifice time.**
870.6200	Neurotoxicity screening/ Subchronic neurotoxicity	43616516 (1993) **Acceptable/Guideline** 0, 100, 750, 1500, or 3000 ppm, M: 0, 6.54, 47.6, 102, or 224 mg/kg/day F: 0, 8, 59.9, 137, or 333 mg/kg/day	No effects on the functional observation battery, or motor activity were observed. No treatment-related gross or microscopic findings in the nervous system or skeletal muscles of the male and female rats were observed. **The Neurotoxicity NOAEL ≥3000 ppm (224 mg/kg/day in males and 333 mg/kg/day in females; HDT).** **Neurotoxicity LOAEL was not established.**
870.6300	Developmental neurotoxicity (rat)	45377901 (2001) **Acceptable/Non-guideline** 0, 5, 50 or 100 mg/kg/day	**Maternal Toxicity NOAEL = 50 mg/kg/day** **Maternal Toxicity LOAEL = 100 mg/kg/day**, based on slight decrease body weight, body weight gains (17%) and food consumption. **Offspring NOAEL = 50 mg/kg/day** **Offspring LOAEL = 100 mg/kg/day**, based on decreased pup survival, decreased pup weight and body weight gain during early lactation (less than 6%), increases in morphometric measurements (anterior/posterior cerebrum for males, cerebellar height for females) at PND 79-83, and decreased retention in the water maze task for adult females (latency 158% of control levels) seen at the LOAEL of 100 mg/kg/day.
870.7485	Metabolism and pharmacokinetic (rat)	43616530 & 43616531 (1994) **Acceptable/Guideline** [2-^{14}C]cymoxanil (98% a.i.) was administered to male and female Crl:CD/BR rats (3-5 animals/sex/dose) by gavage as a single dose at levels of 2.5 or 120 mg/kg, or as a single dose (2.5 mg/kg) following a 14-day pretreatment with unlabeled cymoxanil (2.5 mg/kg/day).	Cymoxanil was readily absorbed and 86 to 94% of the administered dose was excreted in 96 hours. The majority of the administered dose was recovered in the urine (64 - 57%) with smaller amounts excreted in the feces (16 - 24%) and carcass (< 1%). There were no sex-related differences in the absorption, distribution and metabolism of cymoxanil. In urine about 37 - 55% of the dose was free and/or conjugated [^{14}C]glycine and 2 cyano-2-methoxyiminoacetic acid (IN-W3595; about 7 to 33% of the dose). Intact cymoxanil was not isolated in urine. In feces intact [^{14}C]cymoxanil (< 1%) and IN W3595 was detected, but the majority of radioactivity was [^{14}C]glycine (about 9 - 13%). Based on the data, the metabolic pathway involves hydrolysis of cymoxanil to IN W3595, which is then degraded to glycine, which in turn is incorporated into natural constituents or further metabolized.
870.7800	Immunotoxicity (rat; dietary)	44944601 (1999) **Acceptable/Guideline** 0, 200, 400, 800, or 1600 ppm [equivalent to 0/0, 14/16, 27/31, 54/59, or 108/117 mg/kg bw/day (M/F)]	NOAEL = 108/117 (M/F) mg/kg/day LOAEL not observed.
870.7800	Immunotoxicity (mouse; dietary)	44944602 (1999) **Acceptable/Guideline** 0/0, 30/30, 300/300, 600/1200, or 1200/2400 ppm (equivalent to 0/0, 5/7, 56/71, 108/269, or 218/552 mg/kg bw/day) (M/F)	NOAEL = 218/552 (M/F) mg/kg/day LOAEL not observed.

Appendix B: Metabolism Assessment

Table B.2. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Matrix	Percent TRR (PPM) [1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Cymoxanil (2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide, E isomer)	Lettuce		2.1 (0.23 ppm)	
	Potato	None	None	
	Tomato	None	1.1 (0.01 ppm)	
	Grape	None	None	
	Rotational Crops	None	None	
	Ruminant	None	None	
	Poultry	NA	NA	
	Rat	None	None	
IN-KQ960 (3-ethyl-4-(methoxyamino) -2,5-dioxo-4-imidazolidinecarboxamide)	Lettuce		7.4 (0.80 ppm)	
	Potato	None	None	
	Tomato	None	None	
	Grape	None	None	
	Rotational Crops	None	None	
	Ruminant	None	None	
	Poultry	NA	NA	
	Rat	None	None	
IN-KP533 ([[Ethylamino)carbonyl]amino]oxoactiec acid.)	Lettuce		2.8 (0.31 ppm)	
	Potato	None	None	
	Tomato	None	None	
	Grape	None	None	
	Rotational Crops	None	None	
	Ruminant	None	None	
	Poultry	NA	NA	
	Rat	None	None	
Lettuce, 44944605, 3.0 lb ai/A; 5x; 3 days. *Tomatoes, 43616532, 1.69 lb ai/A, 6x; 3 days.* *Potatoes, 44180755, 1.36 lb ai/A, 3days.* *Goats; 12345678; 10 ppm; 25X MTDB; 5 days; 12 hour PSI.* *Rotational Crops; 1.08 lb ai/A, 1.3x, applied to sandy loam soil;30-120 day PBI* *Rat Metabolism; 2.5 or 120 mg/kg gavage dose; Crl:CD/BR.*				

Appendix C: Tolerance Reassessment Summary and Table

Table C.1. Tolerance Summary for Cymoxanil.			
Commodity	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
Leafy greens, subgroup 4A	19	19	A tolerance for leafy greens (subgroup 4A) should be established concomitant with the revocation of individual tolerance for head lettuce.

Leaf petioles, subgroup 4B	6	6	The recommended subgroup tolerance is based on adequate data from celery.
Cilantro, leaves	19	19	As per Agency Guidance Review (2006), the commodity definition for cilantro leaves is equivalent to parsley leaves and the tolerance for leafy greens (subgroup 4A) may be translated to include cilantro leaves.
Vegetable, bulb, group 3	1.1	"Onion, bulb, subgroup 3-07A" at 0.05 ppm "Onion, green, subgroup 3-07B" at 1.1 ppm	The available data suggest that a tolerance for bulb vegetables (crop group 3) is inappropriate because of the wide variability in field trial residues among the representative commodities. The available data will, however, support subgroup tolerances of 1.1 ppm for "Onion, green, subgroup 3-07B" and 0.05 ppm for "Onion, bulb, subgroup 3-07A".
Chive, fresh leaves	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Chive, Chinese, fresh leaves	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Daylily, bulb	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A" will cover expected residues resulting from the proposed use.
Elegans, hosta	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Fritarillia, bulb	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A" will cover expected residues resulting from the proposed use.
Fritarillia, leaves	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Garlic, Serpent, bulb	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A" will cover expected residues

			resulting from the proposed use.
Kurrat	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Lady's Leek	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Leek, wild	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Lily, bulb	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A" will cover expected residues resulting from the proposed use.
Onion, Beltsville bunching	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Onion, Chinese, bulb	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A" will cover expected residues resulting from the proposed use.
Onion, fresh	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Onion, macrostem	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Onion, pearl	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A" will cover expected residues resulting from the proposed use.
Onion, potato, bulb	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A" will cover expected residues resulting from the proposed use.
Onion, tree, tops	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Shallot, bulb	1.1	Not needed	The recommended tolerance for "Onion, bulb, subgroup 3-07A"

			will cover expected residues resulting from the proposed use.
Shallot, fresh leaves	1.1	Not needed	The recommended tolerance for "Onion, green, subgroup 3-07B" will cover expected residues resulting from the proposed use.
Caneberry, subgroup 13A	4.0 ppm	4.0 ppm	Tolerances were recommended and subsequently established for caneberry, subgroup 13A (DP Num: 333252, D. Rate, 06/FEB/2007). The Section F must be revised requesting tolerances on Caneberry, subgroup 13-07A.

Table C.2. International Residue Limit Status

Chemical Name: [2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino)acetamide]	Common Name: Cymoxanil	X Proposed tolerance □ Reevaluated tolerance □ Other	Date: 04/02/2008

Codex Status (Maximum Residue Limits)	U. S. Tolerances
√ No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number: 7E7282, 7E7283 DP Barcode: 349395 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: Debra Rate / RIMUERB / RD
	Residue definition: cymoxanil [2-cyano-N-[(ethylamino)carbonyl]-2-(methoxyimino) acetamide]

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Leafy greens, subgroup 4A	19
		Leaf petioles, subgroup 4B	6
		Cilantro, leaves	19
		Vegetable, bulb, group 3	1.1
		Chive, fresh Leaves	1.1
		Chive, Chinese, fresh leaves	1.1
		Daylily, bulb	1.1
		Elegans hosta	1.1
		Fritarillia, bulb	1.1
		Fritarillia, leaves	1.1
		Garlic, Serpent, bulb	1.1
		Kurrat	1.1
		Lady's Leek	1.1
		Leek, wild	1.1
		Lily, bulb	1.1
		Onion, Beltsville bunching	1.1
		Onion, Chinese, bulb	1.1

Table C.2. International Residue Limit Status			
		Onion, fresh	1.1
		Onion, macrostem	1.1
		Onion, pearl	1.1
		Onion, potato, bulb	1.1
		Onion, tree, tops	1.1
		Shallot, bulb	1.1
		Shallot, fresh leaves	1.1

Limits for Canada	Limits for Mexico
□ No Limits √ No Limits for the crops requested	□ No Limits √ No Limits for the crops requested
Residue definition 2-cyano-*N*-[(ethylamino) carbonyl]-2-(methoxyimino) acetamide	Residue definition: cymoxanil

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions: S. Funk, 04/02/2008.

Appendix D: Review of Human Research

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.